Herbal Medicine

Crossiroads

"My secret," said Ibu Nining, an Indonesian forestry administrator, "is jamu. It gives me energy." A growing cadre of urban professionals like Nining have sent sales of jamu, traditional Javanese herbal medicine, through the roof. Worldwide, the use of herbal medicine has risen dramatically. In countries like Indonesia, the surge has come with growing urban markets for traditional products. In the United States, the rising popularity of herbal medicines has been ascribed to a broad search for a more "natural" health system and dissatisfaction with current health care and its costs. Media attention has focused mainly on the novelty of these products from a conventional medical perspective, not on the effects of and reasons for this rising demand on quality standards and supply.

The World Health Organization estimates that up to 80% of the world's population relies on traditional medicinal systems—not Western medicine—and in many of these systems herbal medicine plays a key role. In the United States, according to a survey published in the *New England Journal of Medicine* in 1993, nearly one in three Americans surveyed use some kind of alternative medical treatment.

In the past year and a half, U.S. debate over herbal medicines has arisen again, fueled by legislation that moves closer to acknowledging the role of herbal medicines as a complement to Western medicine. On the one hand, a 6 May 1996 Newsweek cover story announced the dangers of an unregulated herbal drug industry. The article followed an FDA warning against all products containing ephedra—a stimulant derived from Ephedra sinica used to control weight and boost energy— and the report of

at least one death. On the other hand, James Gordon, professor of family medicine at Georgetown University and chair of the program advisory council to the NIH Office of Alternative Medicine has published a new book, Manifesto for a New Medicine, that he describes as a primer for physicians as well as the public on how to use complementary forms of medicine, including herbal medicines, as tools in a new partnership for health. "In one sense, that kind of attention is fine," says Gordon of the Newsweek article. "We all need to become more attentive to what we do." The article, he notes, confirms the growing importance of herbal products and the fact that Americans are just now approaching a better understanding of them.

Regulation

As herbal medicine use has increased, countries have wrestled with the need to regulate these products for public safety. In Japan, where only physicians practicing Western medicine are licensed, the growing popularity of kampo (Japanese herbal medicine in the Chinese tradition) has challenged the medical system. Kampo, the primary form of medicine in Japan up to the mid-1800s, is less targeted against disease than Western medicine, and in fact, does not assign names to diseases; nonetheless, scientific studies have confirmed the effectiveness of some kampo remedies. In the 21 August 1993 issue of The Lancet, Catrien Ross reported that 70% of Japan's more than 200,000 doctors (including all doctors aged 30-40

who were surveyed) prescribed *kampo* drugs in their daily practice. Following recognition by the Japanese Association of Medical Sciences, it was announced that medical schools would grant degrees in the practice of *kampo*.

Germany, Europe's leading importer of herbal medicinal products, has perhaps the most experience regulating their trade. In 1989, a product from Ginkgo biloba, often used for tinnitus, was the most widely used medicine in West Germany, where more than 5 million prescriptions were written. The German herbal product market has grown from an estimated \$1.7 billion in 1989 to \$3 billion in 1995. To monitor these products, the German government has prepared monographs defining quality standards and potency tests for over 350 singleplant drugs. Known as the Commission E monographs, they include descriptions of uses, contraindications, side effects, and dosages.

France has also officially recognized more than 200 medicinal plants and provided specifications governing their sale. To advance the state of herbal medicine, European trade associations formed the European Scientific Cooperative for Phytotherapy (ESCOP) under the auspices of the European Economic Community (EC). ESCOP is publishing a series of plant species monographs for EC marketing authorization.

The British appear to be moving in the same direction. The 22 April 1995 issue of the *British Medical Journal* included an article suggesting that special licensing of herbal medicines for treatment of minor illnesses may be the best way to safeguard public health. Peter A. G. M. De Smet, a Dutch

pharmacist, wrote that the aim of safeguarding public health "is not well served when the stringent application of conventional criteria to herbal medicine-like products leaves most such products outside strict regulatory control." The article suggested practitioners should be licensed with the obligation to report adverse reactions, and that mechanisms for postmarketing surveillance be

In the United States, regulation of herbal medicine-type products changed in 1994 with the passage of the Dietary Supplement Health and Education Act (DSHEA). This law reclassified herbal products, along with vitamins and minerals, as dietary supplements—a category somewhere between food and over-the-counter drugs. Under the DSHEA law, a manufacturer may make structure-function claims for a product on its label, provided these claims are supported by scientific evidence. This places the burden of proof on the FDA to show that a product poses danger before it can restrict sales.

In January 1996, following a schedule set forth in the new law, the FDA proposed new labeling rules for dietary supplements, including herbal medicinal products. The standards would follow the same basic format as for processed foods regarding nutritional information, but would permit product labels to list "nonessential dietary ingredients, such as herbs." The rules are expected to be finalized and in effect by early

Federal Research

The consequences of the DSHEA for federal

research on herbal products is not yet clear. The FDA's role is still to supervise, but not conduct, clinical trials of new medicines, according to Brad Stone, an FDA spokesman. The FDA does not determine the nature of the clinical methods or what products to study, although it does review research plans for scientific and ethical standards.

In late 1995, the FDA examined adverse reaction reports to determine whether herbal products containing ephedra should be restricted. In April 1996, the FDA issued a warning on ephedra-containing dietary supplements sold as a substitute for "street drugs." The statement cautioned consumers not to

buy ephedra-containing products that are packaged as safe and natural substitutes for illegal drugs such as "ecstacy," because they can have "potentially dangerous effects on the nervous system and heart."

The FDA warning suggests that the need for the agency's investigations to proceed case by case have slowed the regulatory process. To get past the product-by-product backlog, the FDA has published consumer information on some of the broader issues, such as how to choose alternative medical treatments.

When Newsweek published its cover story a month after the April FDA warning, it focused on the lack of

strict regulation and cases of abuse, especially that of a 20-year-old college student who died shortly after taking eight pills of an ephedra product. And although the article ended with recognition that the risk from these products is small relative to prescription drugs, it suggested that the FDA had dropped the ball in its failure to press quickly for mandatory warning labels.

A number of federal agencies conduct research related to herbal medicines, with differing mandates. These include the National Toxicology Program (NTP), the FDA's National Center for Toxicological Research, and the National Cancer Institute

(NCI). NTP studies focus mainly on potential public health risks like genetic toxicology (including mutagenicity) and longterm effects including cancer risks. These studies are typically coordinated with all regulatory agencies that aim to protect worker, consumer, and environmental health. The EPA, for example, uses NTP studies in its regulation of insecticides and pesticides.

James Huff, a researcher with the NIEHS (where the NTP is located), estimates that onethird of the 450 chemicals the NTP has tested for carcinogenicity are "natural" chemicals, but not necessarily herbal medicines. For example, the NTP studied



Purple Coneflower (Echinacea purpurea)

Origin: Europe Uses: Treating flus and colds, stimulating immune system. Studies: The subject of more than 350 studies, echinacea seems to stimulate growth and development of immune system cells and exhibits interferonlike antiviral activity.

teas (as well as a contaminant in honey, meat, grains, and milk) was the subject of short-term toxicity studies in 1993 and was found to cause cancer in rats after only 13 weeks of exposure. The FDA's National Center for Toxicological Research conducts studies mainly on the biological mechanisms of action

underlying the toxicity of

products regulated by the

FDA, according to spokes-

ephedrine sulfate in

1986, and found no evi-

dence of carcinogenicity

in experimental animals.

Riddelliine, a naturally

occurring pyrrolizidine

alkaloid in some herbal

man Victor Attwood. In coordination with the NTP, the center conducts bioassays on specific compounds, but generally

has not studied herbal medicines. In the course of monitoring endangered species, the Forensic Laboratory of the U.S. Fish and Wildlife Service studied imported herbal products for components derived from endangered species, such as bear bile and musk excretion. Evidence of the rare species were seldom present, says the laboratory's deputy director, Ed Espinoza, but they found that the products did contain arsenic and mercury. In September 1995, Espinoza and his colleagues reported their findings in the New England Journal of Medicine, noting that by taking the dosage recommended on the label of a Chinese herb ball product, an adult could consume up to 73 mg of arsenic, and more than 1200 mg of mercury dailymore than four times the amount reported to cause chronic mercury sulfide poisoning. "Health care professionals should be aware that patients who consume traditional Chinese remedies may be exposed to many potentially toxic substances," they wrote. The same may be said of pharmaceutical drugs, of course; the main difference is that for herbal remedies, methods for assessing ingredients and labeling products have not yet been standardized.

Most federal research that scientifically evaluates potential medicines takes place at the NCI. The institute's ongoing program for screening natural products for anticancer and anti-AIDS properties tests samples of plants, herbs, microbes, and marine life against 60 types of human cancer and the AIDS virus. It's an early step in the process that leads to clinical trials and FDA approval as a drug.



Milk thistle (Silybum marianum)

Origin: Europe

Uses: Has been used for 2,000 years to prevent and repair liver damage. Studies: Helps regenerate liver cells damaged by alcohol and diseases such as hepatitis and cirrhosis. In animal studies, it protected against radiation damage from X-rays and the nerve toxin triethyltin sulfate.

Within the National Institutes of Health, principal responsibility for studying herbal medicines lies with the Office of Alternative Medicine (OAM), created in 1991. Through several series of peer-reviewed grants, the OAM set about evaluating therapies as diverse as homeopathy, acupuncture, and music therapy. After the first round of small grants in 1993-1994, the OAM has concentrated on using its grants to foster centers of study.

In December 1994, the OAM published Alternative Medicine: Expanding Medical Horizons, a comprehensive overview of the main fields of alternative medicine and an outline of research needs. The report's section on herbal medicines cites scien-

tific studies from Europe and Asia that confirm health benefits of particular remedies. The report also notes that "the current regulatory mandate puts the FDA in a difficult position. It is expected to 'protect the public' but has no expertise or resources to evaluate the global herbal medicine inventory . . . Instead of expecting the FDA to be an omnipotent protector, Congress should legislate a more educational, informational role," for example, by establishing certification of herbal content and potency for inclusion on labels.

The American Medical Association's (AMA) position on herbal medicines remains one of wary interest. The AMA encourages physicians to report to the FDA any adverse effects attributed to herbal medications. The association is "very interested" in the OAM-sponsored research, according to AMA press officer James Stacey. However, according to AMA Assistant Director for Media Brenda Crane, the FDA's MedWatch program only allows reports of negative effects. "There is no program for reporting positive effects," she says. "That's just the way the system is set up."

Beneficial Effects Confirmed

For centuries, plant-based folk remedies have provided a basis for Western medicine's pharmaceutical research. The discovery of *Digitalis's* effectiveness as a treatment for cardiac patients started with a folk healer in Shropshire, England, in the 1780s. With the advent of synthetic compounds in the 1950s, however, ethnobotany—the study of the relationships between plants and people—declined as a source of pharmaceutical leads.



Ginkgo (Ginkgo biloba)

Origin: Europe and Asia
Uses: Primarily used in Europe
to treat symptoms of aging.
Studies: Increases brain
tolerance of oxygen deficiency
and increases blood flow.
Improved mobility, orientation,
communication, mental
alertness, and recent memory.
Stimulated circulation and
reduced cardiovascular risks.
Inhibits deteriorating vision in
the elderly.

\$2 million since 1992 to study and conserve tropical forests. Bristol-Myers Squibb, Pfizer, and the NCI have also invested millions in biodiversity prospecting in this decade, usually in tropical forests.

It is widely held that about one quarter of Western medicines are derived from plants, although a recent study led by Francesca Grifo, director of the Center for Biodiversity and Conservation at the American Museum of Natural History, puts the figure closer to 60%. Most Western

plant-derived medicines, however, resulted from isolating active ingredients and not from the complex compounds that make up most herbal remedies. Some scientists apply the term "botanical" to any product that contains ingredients of vegetable matter or its constituents as a finished product.

Research continues to accumulate evidence for and against herbal medicines. Scientific research on many herbal medicines has shown a clear correlation with health benefits. For Ginkgo biloba, for example, the NIH's Alternative Medicine report cites more than nine published scientific studies, conducted mostly in Europe, confirming ginkgo's effectiveness in improving cognitive function and circulation.

In the last decade, ethnobotany has reemerged, with a growing number of scientists being trained and willing to do the needed field work, and more sophisticated technology available for bioassays. Such bioassays can now test plant compounds quickly against a wide range of human diseases. These technological advances have also fueled investment in "biodiversity prospecting," a wider approach than ethnobotany that involves performing broad inventories of species in diverse ecosystems. The most publicized biodiversity prospecting agreement, between Merck Pharmaceuticals and Costa Rica.

has involved more than

and in reducing the risk of cardiovascular disease. The report also cites findings confirming the benefits of milk thistle (Silybum marianum, used both to prevent and repair liver damage), saw palmetto (Serenoa repens, effective against benign prostatic hypertrophy), and echinacea (Echinacea purpurea and Echinacea angustifolia, found to have immune-enhancing and antibacterial properties), among others.

Some remedies have been proven to have targeted effects against serious health risks. Sho-saiko-to (a Japanese kampo medicine composed of parts of Bupleurum falcatum, Pincilia ternata, Scutellaria baicalensis, Panax ginseng, Zizyphus jujuba, Blycyrrhiza uralensis, and Zingiber officinale) was found by researchers at Osaka City General Hospital to correspond with lower rates of liver cancer among cirrhosis patients. The study by Hiroko Oka and colleagues, published in the 1 September 1995 issue of Cancer, looked at 260 cirrhosis patients over 5 years; half were given Sho-saiko-to and conventional medicines, while the other half received only the conventional treatment. Only 23 (17.7%) of the Sho-saiko-to recipients developed liver cancer, compared to 33 (25.4%) of the patients receiving conventional treatment.

Adverse Reactions

Apart from occasional cases of intentional abuse, adverse physical reactions to botanical products are usually caused by adulteration or contamination of products during preparation or packaging, or mistaken plant identification in cases of self-treatment. Recent

reports have shown potential negative effects of chaparral (*Larrea tridentata*) and certain herbal teas, in addition to the ephedrine products and imported herb balls mentioned above.

A letter exchange in the 20 September 1995 issue of the Journal of the American Medical Association highlights the need for more precise descriptions as a first step toward understanding botanical remedies unfamiliar to Western medicine. Several letters criticized an article on the possible liver toxicity of chaparral for its vague use of the common name "chaparral" and for implying that it is an herb, rather than a woody perennial shrub. In reply,



Ginger rhizome (Zingiber officinale)

Origin: China
Uses: Used to treat seasickness, nausea, and diarrhea.
Studies: Ginger has been shown to be effective against motion sickness and morning sickness, although no studies have been done for effects on the fetus. In China it was effective in treating acute bacillary dysentery and acute orchitis (inflammation of the testes).

the article's authors agreed that "more careful attention to plant taxonomy is appropriate" among physicians "because of the growing use of alternative remedies.'

Research Hurdles

When medical systems collide, conventional methods for studying efficacy may no longer apply. Western medicine's search for active ingredients is thwarted by the chemically complex nature of botanical remedies-proponents say that the activity of a remedy's ingredients is synergistic and balanced for a therapeutic effect greater than that of any individual ingredient. "The research on herbs tells us that each has specific chemicals with specific effects," observes Gordon in his book. "It doesn't, however, begin to address the question of the correspondences between the Chinese theory of their action and the Western chemical analysis."

Besides these technical issues, proponents who would like to see herbal medicines treated as drugs also point to the financial barriers. The years of clinical trials required for FDA drug approval can cost \$100-500 million for a single drug-feasible for large pharmaceutical corporations with patentable products, but not for small manufacturers of herbal products without clear patent protection.

A further institutional problem is the apparent lack of a framework that documents both health benefits and toxicity risks. The FDA issues statements mainly to warn the public against potential health risks. Health care providers and the public, however, desire substantiated reports about potential benefits,

many of which have appeared in journals in Europe but not in America. There appears to be no database in English that catalogs risks of herbal medicines together with documented remedies. To address this need, the American Botanical Council, a nonprofit research organization based in Austin, Texas, will publish a translation of the German Commission E monographs this fall.

Still, opposing sides appear to be converging. The nonprofit National Council Against Health Fraud (NCAHF) put forward labeling recommendations in its July-August 1995 newsletter. Like the American Botanical Council, the NCAHF called for a special category of over-the-counter medicines. While the two

groups differ as to suggested label wording, both propose that labels identify plant sources by their scientific names and include a toll-free telephone number for consumers to report adverse reactions. The NCAHF cautions consumers to buy only those products that identify plant species and state contraindications, and to consult a physician before using an herbal therapy while taking other medication.

Other countries' experiences in integrating Western and traditional herbal medical systems show a pattern of dialogue and gradual institutional change. In Sri Lanka, where the ancient Indian practice of Ayurvedic med-

icine coexists with Western medicine, the process started in 1929 when the British colonial administration established a separate College of Indigenous Medicine. By the late 1950s, the Sri Lankan Health Ministry had a department devoted to promoting Ayurveda, and in the 1970s, the College of Ayurveda became affiliated with the University of Colombo. Ayurvedic practitioners in Sri Lanka are required to have a license, and traditional Ayurvedic knowledge is being catalogued with government and United Nations support. Public hospitals and over 300 cen-

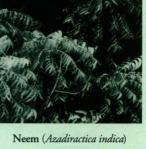
> tral dispensaries now provide Ayurvedic treatment, according to Upali Pilipitiya, director of the Bandaranaike Memorial Avurvedic Research Institute, which conducts clinical research on Ayurvedic medicine's effects against rheumatoid arthritis, diabetes mellitus, bronchial asthma, leukoderma, psoriasis, and chronic headaches.



Lobelia (Lobelia cardinalis)

Origin: Native American Indian Uses: Treating ulcers and stomachache, syphilis, colds, nosebleeds, fever, and rheumatism.

Studies: No systematic studies have been done on this herb's effects, although another lobelia variation (Lobelia inflata) yields lobeline sulfate, which is used in antitobacco therapy.



Origin: India and Africa Uses: Used together with turmeric to treat chronic ulcers, eczema, and scabies. Neem tea is drunk as a tonic. Studies: Used as a paste in one study to treat scabies in 814 people, it cured 97% of cases in 3-15 days with no adverse reactions. It may also have anticancer properties.

(AP) reported that, with a new law, Vermont became the eleventh state to license naturopaths. Naturopathy is a broad category that includes practitioners of herbal remedies along with those of other nonsurgical, nondrug treatments like manipulation. The Vermont law requires candidates for licensing to complete four years of postgraduate university study, as required in conventional Western medical training. Also, as in conventional medical training, the first two years must focus on standard human biology. Recognition by medical insurance, however,

help the public distinguish

careful practice from quack-

ery. In a 26 May 1996 arti-

cle, the Associated Press

remains rare. According to the AP, some smaller insurance companies cover naturopathic treatment, but most do not.

With the enactment of the DSHEA, a series of seminars has brought together a variety of concerned U.S. professionals for the first time. In March 1995, FDA officials met with more than 100 herbal medicine providers, manufacturers, growers, and researchers to examine the role of botanical products in health care worldwide. A followup seminar held in April 1996 focused on scientific issues related to multicomponent botanical products. Both seminars were sponsored by the nonprofit Drug Information Association with OAM and

The most recent workshop addressed questions of botanical quality, purity, and characterization. These technical issues provide a common language for chemists and botanists from different constituencies to discuss herbal medicine. The 151 participants at the April seminar came from universities, botanical manufacturers, the FDA, and the over-the-counter and prescription drug industries.

Another seminar, planned for early 1997, will pursue issues of appropriate dosage and efficacy, which methodologies should be used to evaluate the effectiveness of botanical products, and how researchers can decide whether to study a botanical product as a compound or search for single active ingredients.

With this forum for both regulators and medicine manufacturers, a new framework may be emerging. According to Floyd Leaders, a pharmacologist and former OAM

complementary medicine in the United States have sought the opportunity to register with authorities, like their counterparts in Sri Lanka. For them, licensing would set a standard of accountability by which they could be judged, and which would

More Signs of Change

For years, practitioners of

liaison with the FDA, the dialogue generated by the first botanical-related OAM grants has led to two significant changes in the FDA policy governing botanicals being considered as drugs. First, there appears to be a growing willingness to reconsider the "contribution to efficacy" requirements, which obligate manufacturers to demonstrate the contribution of each chemical component of a single botanical. For example, says Leaders, "Now the FDA seems willing to look at ginseng as ginseng."

The second policy shift relates to the animal toxicology testing routinely required for a new product before clinical trials can

begin. For botanical products already widely used by humans, the need for these tests could be relaxed, as they have been for several OAM grant studies on herbal products.

Freddie Ann Hoffman, deputy director of the medicine staff in the FDA's Office of Health Affairs, who chairs a new internal FDA working group on botanical products, agrees that these seminars have "opened a novel opportunity for the FDA, the NIH (OAM), industry, and academia to . . . develop the scientific support required to expand the range of products available" in the United States. In an article coauthored with Leaders in the January/February 1996 issue of Pharmaceutical News, Hoffman concluded that recent policy changes differ "significantly from previous [drug approval] policy" and provide a basis for broader policy review within the FDA.

A Resource under Pressure

With a growing global market, the sources of herbal medicines are coming under intense pressure. For example, Indonesia has seen an explosive increase in demand, and a distressing effect on wild plant populations in forests. In the last 20 years, the expanding herbal medicine industries have pried open a huge market using quality packaging and advertising, notes Satyawati Hadi, a scientist at the Forest Products Research and Development Center in Bogor, Indonesia. The industries' consumption of symplicia (dried natural medicinal materials) has grown from 59 tons in 1972 to 7,784 tons in 1992. "Continuous harvesting without establishing plantations may result in the extinction of some of the species," Hadi cau-



tions. Hadi and others urge more regulated harvests, increased cultivation, and an equitable sharing of profits, which encourages conservation by collectors.

The supply problem is by no means limited to developing countries. In the United States it is compounded by a lack of research on plant properties. "Most American medicinal plants have yet to be thoroughly investigated in terms of pharmacology and chemistry," Steven Foster and James Duke note in A Field Guide to Medicinal Plants: Eastern and Central North America. "Visiting European and Chinese medical botanists . . . caution that we should conserve [our wild herbs].'

American ginseng harvests are regulated by law, but that has not prevented a dangerous rise in harvests of wild ginseng plants from forests as prices have soared. For states like Virginia and West Virginia, the evidence suggests that harvests have already outstripped the natural productivity of these populations. Species of echinacea are similarly threatened.

Some suggest that such alarms are overstated, that in fact the market demand for a particular species fuels the search for resolution of any shortage. The February 1996 issue of Fortune examined the sequence of events in which taxol from the Pacific yew (Taxus brevifolia) was found to be effective against ovarian cancer, then endangered by the harvests needed for research and development. It was finally rescued by research that discovered a semisynthetic version, involving a hybrid yew that could be grown on plantations. "[T]he next time the newspapers are full of a seemingly insoluble problem," noted the article, "consider what the market might do to help solve it."

Nevertheless, between the perception of a supply shortage and its resolution, a popular species could become extinct; it can take seven years to grow a harvestable ginseng root. In the case of taxol, a self-imposed harvest limit probably helped prevent this. An article in the April 1996 issue of *Environmental Health Perspectives* noted the public health consequences of biodiversity loss in a case where the NCI harvested the entire known adult population of a shrub containing the anticancer compound maytansine.

An "early warning" system based on

projections of growing demand and existing production capability (both natural and cultivated) could signal which species require urgent action. "Putting together a list of priority species and those subject to depletion would not be too difficult," says Robert McCaleb, director of the Herb Research Foundation in Boulder, Colorado. While biodiversity loss and its consequences for botanical medicines has yet to enter the public debate over these products, it could be a rallying point for resource conservation as well as for public health planning.

Educating the public is crucial. "Consumers need to be aware that there are environmentally sound ways and irresponsible ways to collect these products," says McCaleb. With this awareness, the public can influence harvesting methods. For example, almost all cultivated echinacea is *E. purpurea*, says McCaleb, while almost all *E. angustifolia* is harvested from the wild. By buying only *E. purpurea* products, consumers can encourage cultivation.

This example underscores the widely agreed-upon need for better consumer information, including more detailed product labels. Other countries' experiences and new technologies for chemical characterization appear to be leading the United States toward the scrutiny and integration of knowledge on herbal medicines that it has resisted.

"We need good science to support these products," says Leaders. "Now we're at the stage to consider, 'What is good science? Is this the best way to test these products?'" With growing market demand for reasonably priced and time-tested medicines, and with the legislative prodding of the DSHEA, the U.S. medical and regulatory systems are being forced to address this very question. In the meantime, more precise labels and a better informed public would mark a step toward safely sharing Ibu Nining's secret.

David Taylor

Graphic text source: Alternative Medicine: Expanding Medical Horizons. A Report to the National Institutes of Health on Alternative Medical Systems and Practices in the United States, prepared under the auspices of the Workshop on Alternative Medicine, Chantilly, Virginia, September 14–16 (1992).

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